Imatinib as a novel therapeutic approach for fibrotic disorders

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Editorial

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Imatinib mesylate is a small molecule that binds to the ATP-binding pocket of Abelson kinase (c-Abl) and blocks efficiently its tyrosine kinase activity. c-Abl is an important downstream signalling molecule of TGF-β [1]. The importance of c-Abl for the pro-fibrotic effects of TGF-β is emphasized by the observation that the induction of extracellular matrix proteins by TGF-β is strongly decreased in cells deficient for c-Abl. In addition to its effects on c-Abl, imatinib blocks the tyrosine kinase activity of PDGF receptors. Thus, imatinib targets simultaneously and also rather selectively TGF-β and PDGF signalling, two major pro-fibrotic pathways in SSc [2].

Imatinib is widely used for the treatment of bcr-Abl-positive chronic myelogenous leukaemia (CML) and gastrointestinal stromal tumours with more than 100 000 patients treated so far. Imatinib possesses favourable pharmacokinetics: (i) it is readily absorbed after oral administration; (ii) one dose per day is sufficient, because of the long half-life of imatinib [2]. Imatinib is generally well tolerated and severe adverse effects are rare. However, less severe side-effects are common and might lead to discontinuation in 15–30% of the patients outside of clinical trials [3]. The major adverse events of imatinib are often dose-dependent and include oedema, muscle cramps, diarrhoea and bone marrow toxicity [3, 4]. Abl-kinase inhibitors might also increase slightly the risk of congestive heart failure [5, 6].

Pre-clinical evidence for the anti-fibrotic effects of imatinib

We demonstrated that imatinib inhibited dose-dependently the synthesis of collagen 1a1, collagen 1a2 and fibronectin-1 of SSc fibroblasts by up to 90% in pharmacologically relevant concentrations [7]. No compensatory changes of the expression of tissue inhibitors of matrix metalloproteinases (TIMPs) and MMPs were observed. Furthermore, imatinib efficiently reduced the development of fibrosis in the mouse model of bleomycin-induced dermal fibrosis. Treatment of mice with imatinib at doses of 50 mg/kg/day and 150 mg/kg/day had strong anti-fibrotic effects. Imatinib prevented the differentiation of resting fibroblasts into myofibroblasts and reduced dose-dependently the synthesis and accumulation of extracellular matrix in lesional skin.

Apart from SSc, imatinib has also been shown to be effective in models of pulmonary fibrosis, renal fibrosis and liver fibrosis [1, 8–10]. In all of these models, imatinib prevented the development of fibrosis, when initiated at the onset of the fibrotic stimulus.

We demonstrated recently that imatinib can also induce regression of pre-existing dermal fibrosis. To evaluate the efficacy of imatinib for established fibrosis, a modified model of bleomycin-induced fibrosis was used. In this model, mice were challenged with imatinib for 6 weeks and subgroups of mice were additionally treated with imatinib for the past 3 weeks. Treatment with imatinib not only prevented further progression of dermal fibrosis despite ongoing injections of bleomycin, but also induced regression of fibrosis below the levels of mice challenged with bleomycin for 3 weeks [11].

We also showed that dasatinib and nilotinib, two novel and more potent inhibitors of Abl-kinases, and PDGF receptors, which are approved for the treatment of Bcr-Abl-positive chronic myelogenous leukaemia with resistance or intolerance to imatinib, also have potent anti-fibrotic effects *in vitro* and *in vivo* [2]. As the spectra of adverse effects of dasatinib and nilotinib differ from that of imatinib, patients with intolerance to imatinib can often be switched safely to nilotinib or dasatinib. Thus, dasatinib and nilotinib might be interesting candidates for the treatment of patients that cannot tolerate imatinib.

Clinical outcome of first patients with fibrotic diseases

Sabnani and coworkers [12] report in this issue of *Rheumatology* five patients with SSc-related interstitial lung disease (SSc-ILD) treated with a combination of imatinib and cyclophosphamide. All but one patient had severe, end-stage SSc-ILD with a <25% predicted diffuse capacity for carbon monoxide (DL_{CO}). The forced vital capacity (FVC) was <50% predicted in three patients and three patients were too ill to perform a 6-min walking test. All patients had previously received immunosuppressants, including oral cyclophosphamide in three patients. Thus, the patients reported by Sabnani *et al.* were critically ill with end-stage disease that had been progressive despite several therapeutic attempts. These patients were treated with intravenous pulses of 500 mg cyclophosphamide every 3 weeks and oral imatinib in various doses. One patient received 100 mg, two received 200 mg and two patients started with 200 mg for 6 months and then received 400 mg. The follow-up time and the duration of the treatment were different for the five patients and ranged from 3 to 18 months.

Imatinib was well tolerated by all patients and major treatment-related adverse effects did not occur. In particular, none of the patients developed clinical evidence of congestive heart failure, although echocardiography or repeated heart catheterization was not performed. Fluid retention was mild and required diuretics in only one patient. Three patients showed mild reductions in haemoglobin levels and erythropoietic stimulating agents were given.

The outcome of the patients was different. One patient, who was suffering from severe other comorbidities, such as left ventricular dysfunction, died within 3 months before the first follow-up. In one patient, the DL_{CO} remained stable, but FVC and total lung capacity (TLC) decreased slightly and the patient underwent lung transplantation after 6 months. One patient, who had the worst lung function parameters initially, died after 12 months of therapy. Within this period, his DL_{CO}, FVC and TLC remained stable. Improvement was observed in two patients. One patient experienced a mild increase in all lung function parameters. The other patient improved by 26% in DL_{CO}, but not in FVC and TLC. Additional information on morphological changes on high-resolution computed tomography (HRCT), changes in 6-min walking distance, New York Heart Association (NYHA) classification, Borg dyspnoea index, scleroderma HAQ (SHAQ) or arterial oxygen saturation were not mentioned.

When interpreting the results of this study, one has to keep in mind that imatinib was underdosed in this study. All patients received only 100 or 200 mg of imatinib for the first 6 months. The doses of imatinib for the treatment of CML and gastrointestinal stromal tumours (GIST) range from 400 mg/day to 800 mg/day. Although the number of patients was small and this might have been by chance, it is striking that the two patients, who improved during treatment, received imatinib in normal doses of 400 mg/day during the second half of the study. Thus, the doses of imatinib might have been subtherapeutic and imatinib might exert more potent anti-fibrotic effects in standard doses. However, most

adverse events of imatinib are dose dependent, and thus the rate of adverse effects might increase with higher doses of imatinib. Another interesting observation is that two of the three patients, who had previously been unresponsive to treatment with cyclophosphamide alone, improved moderately under the combination of cyclophosphamide plus low-dose imatinib.

There is also preliminary clinical evidence from other case reports that imatinib appears to be safe and could be efficacious in fibrotic CTDs. We reported recently the successful treatment of pulmonary fibrosis with imatinib in a patient with MCTD [13]. Before initiation of imatinib, the patient rapidly deteriorated despite treatment with corticosteroids and MTX. However, during the 20 weeks of treatment with imatinib at a dose of 400 mg/day, the patient progressively improved. The NYHA class changed from NYHA IV to NYHA II. The 6-min walking distance increased by 50 m and the DL_{CO} increased from 26% predicted to 45% predicted. The arterial oxygen pressure increased from 64 mmHg to 70 mmHg at rest and from 50 mmHg to 62 mmHg after exertion. Ground glass opacities decreased during treatment, whereas the reticular changes remained constant. However, no changes in FVC and TLC were observed. The patient tolerated the treatment well and did not experience any adverse events.

Van Daele *et al*. [14] reported stabilization of pulmonary fibrosis and improvement of dermal fibrosis in a patient with refractory SSc. Prior to imatinib, the patient experienced progressive dermal and pulmonary fibrosis with increasing honeycombing on HRCT despite treatment with corticosteroids and pulsed cyclophosphamide. Upon initiation of imatinib at a dose of 400 mg/day, her modified Rodnan skin score (mRSS) dropped from 18 to 12 within the first 3 months and remained stable thereafter. Pulmonary function test and findings on HRCT remained stable during the 7 months of treatment with imatinib. Imatinib was well tolerated with only mild periorbital oedema.

Sfikakis and coworkers [15] also reported beneficial effects of imatinib for the treatment of refractory SSc. The patient had severe diffuse SSc with 7-yr duration and had previously been treated with cyclophosphamide, AZA and mycophenolate mofetil. The mRSS before treatment with imatinib was 44. During the 6-month course with imatinib at a dose of 400 mg/day, the mRSS decreased progressively to 33 after 6 weeks and to 28 after 3 months and 6 months. In parallel, contractions decreased and the SHAQ score improved.

Kay and High [16] reported recently impressive responses of two patients with nephrogenic systemic fibrosis. Both patients were treated with imatinib in doses of 400 mg/day. In the first patient, the mRSS decreased from 42 to 16 within 15 weeks. In the second patient, a decrease from 12 to 2 occurred within 12 weeks. In parallel to the mRSS, reduced fibrosis and decreased expression of Type I procollagen was observed in skin biopsies of imatinib-treated patients. Of note, skin thickening rapidly recurred in both patients within a few weeks after imatinib was stopped, probably because of the persistent accumulation of gadolinium. However, both patients responded again, when imatinib was re-introduced.

Smaller case series suggested that treatment of patients with CML might lead to a regression of concomitant bone marrow fibrosis [17, 18]. The anti-fibrotic effect did not correlate with the cytogenetic response, suggesting an effect independent from the suppression of Philadelphia chromosome-positive cancer cells [18].

Conclusions

Due to the potent anti-fibrotic effects *in vitro* and *in vivo* in several pre-clinical animal models of tissue fibrosis, favourable pharmacokinetics, good clinical experience regarding safety and toxicity in other diseases and first promising case reports, imatinib is currently investigated in clinical trials as an anti-fibrotic drug for the treatment of SSc. However, one needs to be cautious in over-interpreting the results of the first case series. The course of SSc is variable with spontaneous regression of dermal fibrosis in several patients. Thus, it cannot be excluded that the regression of fibrosis reported in the mentioned case reports might reflect the spontaneous course of the disease in individual patients and not a response to imatinib. Regarding safety, appropriate outcome measures in particular for cardiotoxicity are necessary in a larger number of patients to exclude relevant side-effects in the SSc population. This is of importance, because the large majority of SSc patients have pre-existing cardiac pathologies, although this rarely manifests clinically. In addition, gastrointestinal side effects might be more frequent in SSc patients because of the gastrointestinal involvement in SSc.

Therefore no definite conclusions regarding safety and efficacy can be drawn from the published case reports. The safety and efficacy of imatinib can only be investigated in larger controlled clinical trials. For these reasons we strongly recommend inclusion of patients with SSc into one of the ongoing clinical trials with imatinib (see www.clinicaltrials.gov for details). We discourage the off-label use of imatinib for routine use in such patients, as long as the toxicity profile in SSc patients is not established and as long as results of the ongoing clinical trials are not available. Moreover, the off-label use of imatinib is limited by the high costs that exceed that of other biologics.

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References

1 Daniels CE, Wilkes MC, Edens M *et al.* Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. J Clin Invest 2004;114:1308–16.
2 Akhmetshina A, Dees C, Pileckyte M *et al.* Dual inhibition of c-abl and PDGF receptor signaling by dasatinib and nilotinib for the treatment of dermal fibrosis. FASEB J 2008.
3 Atallah E, Kantarjian H, Cortes J. Emerging safety issues with imatinib and other abl tyrosine kinase inhibitors. Clin Lymphoma Myeloma 2007;7(Suppl. 3):S105–12.
4 Druker BJ, Guilhot F, O'Brien SG *et al.* Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;355:2408–17.
5 Distler JH, Distler O. Cardiotoxicity of imatinib mesylate: an extremely rare phenomenon or a major side effect? Ann Rheum Dis 2007;66:836.
6 Kerkela R, Grazette L, Yacobi R *et al.* Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med 2006;12:908–16.
7 Distler JH, Jungel A, Huber LC *et al.* Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis. Arthritis Rheum 2007;56:311–22.
8 Abdollahi A, Li M, Ping G *et al.* Inhibition of platelet-derived growth factor signaling attenuates pulmonary fibrosis. J Exp Med 2005;201:925–35.
9 Wang S, Wilkes MC, Leof EB, Hirschberg R. Imatinib mesylate blocks a non-Smad TGF-beta pathway and reduces renal fibrogenesis in vivo. FASEB J 2005;19:1–11.
10 Yoshiji H, Noguchi R, Kuriyama S *et al.* Imatinib mesylate (sti-571) attenuates liver fibrosis development in rats. Am J Physiol Gastrointest Liver Physiol 2005;288: G907–13.
11 Akhmetshina A, Venalis P, Dees C *et al.* Treatment with imatinib prevents fibrosis in different preclinical models of SSc and induces regression of established fibrosis. Arthritis Rheum 2008; in press.
12 Sabnani I, Zucker MJ, Rosenstein ED *et al.* A novel therapeutic approach to the treatment of scleroderma associated pulmonary complications: safety and efficacy of combination therapy with imatinib and cyclophosphamide. Rheumatology 2009;48: 49–52.
13 Distler JH, Manger B, Spriewald BM, Schett G, Distler O. Treatment of pulmonary fibrosis for twenty weeks with imatinib mesylate in a patient with mixed connective tissue disease. Arthritis Rheum 2008;58:2538–42.

14 van Daele PL, Dik WA, Thio HB *et al*. Is imatinib mesylate a promising drug in systemic sclerosis? Arthritis Rheum 2008;58:2549–52.
15 Sfikakis PP, Gorgoulis VG, Katsiari CG, Evangelou K, Kostopoulos C, Black CM. Imatinib for the treatment of refractory, diffuse systemic sclerosis. Rheumatology 2008;47:735–7.
16 Kay J, High WA. Imatinib mesylate treatment of nephrogenic systemic fibrosis. Arthritis Rheum 2008;58:2543–8.
17 Beham-Schmid C, Apfelbeck U, Sill H *et al*. Treatment of chronic myelogenous leukemia with the tyrosine kinase inhibitor sti571 results in marked regression of bone marrow fibrosis. Blood 2002;99:381–3.
18 Bueso-Ramos CE, Cortes J, Talpaz M *et al*. Imatinib mesylate therapy reduces bone marrow fibrosis in patients with chronic myelogenous leukemia. Cancer 2004; 101:332–6.